PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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Docket System —
Status Report ✓
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	26 AUG 2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
ISPH-0672WO	

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US03/18320	10 June 2003 (10.06.2003)	11 June 2002 (11.06.2002)

Applicant

ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Terra C. Gibbs Janice Ford for Telephone No. (571) 272-1600

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ISPH-0672WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/18320	International filing date *(day/month/year)* 10 June 2003 (10.06.2003)	Priority date *(day/month/year)* 11 June 2002 (11.06.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68; A01N 43/04; C07H 21/04; A61K 31/07 and US Cl.: 514/44; 536/24.5, 23.1, 24.33; 435/325, 6, 91.1, 375		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 June 2004 (01.06.2004)	15 August 2004 (15.08.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Terra C. Gibbs Telephone No. (571) 272-1600

Janice Ford for

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/18320

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-25 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 26-28, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/18320

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	5-16	YES
	Claims	1-4	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-16	NO
Industrial Applicability (IA)	Claims	1-16	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-16 meet industrial applicability as defined by PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or use din industry.

Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by Windmeier et al. (Biochemical Pharmacology, 1996 Vol. 51:577-584).
Windmeier et al. disclose cultured fat-storing cells exposed to pentoxifylline (see Table 1). The disclosure, at page 8, lines 22-27, teaches that pentoxifylline is a non-specific phosphodiesterase inhibitor that inhibits the production of IL-12 p35 subunit, but not IL-12 p40 subunit. Therefore, Windmeier et al. anticipates claims 1-4.

Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by Cigolini et al. (Artherosclerosis, 1999 Vol. 143:81-90).
Cigolini et al. disclose human adipose tissue treated with pentoxifylline (see Figure 9). Therefore, Cigolini et al. anticipate claims 1-4.

Claims 1-16 lack an inventive step under PCT Article 33(3) as being obvious over Baker et al. [U.S. Patent No. 6,399,379], in view of Gately et al. [WO 99/37682].
Baker et al. teach antisense modulation of IL-12 p35 subunit in cells or tissues *in vitro* or *in vivo* comprising the administration of antisense oligonucleotides targeted to IL-12 p35 subunit (see Abstract).
Gately et al. teach anti-human IL-12 antibodies that are characterized by specificity to the IL-12 heterodimer, but do not bind to the IL-12 p40 subunit.

It would have been obvious to devise a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of IL-12 p35 subunit, using the method taught by Baker et al., and the motivation of Gately et al. One of ordinary skill in the art would have been motivated to devise a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of IL-12 p35 subunit since Baker et al. explicitly teaches contacting a preadipocyte cell with an inhibitor of IL-12 p35 subunit, which would inherently inhibit the differentiation of an adipocyte cell. One of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotides targeted to IL-12 subunit taught by Baker et al. with the IL-12 antibodies taught by Gately et al. because the IL-12 antibodies have been demonstrated to neutralize the biological activity of IL-12 p35 subunit specifically, as opposed to the IL-12 p40 subunit, since the two exist as a heterodimer.